# Crohn's Disease And Hyperbaric Oxygen: Is There A Link?

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**Introduction**

Hyperbaric oxygen (HBO) has been suggested to be beneficial in inflammatory bowel syndromes, mainly in Crohn's disease, on the assumption that enteric tissue oxygenation is impaired.

Several reports have shown encouraging results on the use of HBO in patients with severe or recurrent perineal CD [1-5]. The role of HBO in the pathogenesis of CD has to be determined in order to explain its therapeutic effect and to invite to more clinical studies on this topic.

**Crohn's Disease (CD)**

CD is a complex disorder of the bowel with chronic transmural inflammation and discontinuous location. The usual-hallmark of the disease is a history of recurrent episodes of abdominal pain, diarrhea, weight loss and fever.

The characteristic lesion of CD is intestinal ulceration, which can occur in any area of the gastrointestinal tract [6-7].

One third of patients, particularly those with colonic involvement present with perianal disease, an especially difficult complication of CD. Patients develop perirectal fissures, fistulas and abscesses due to ulcer extension through the intestinal wall [8]. Recurrent perineal CD can be an extremely debilitating complication, rendering an optimal therapy very difficult.

**CD Pathogenesis**

Current theories on the pathogenesis of CD are:

Inflammatory process, which involves the following steps:

a) An infection, caused by intraluminal microbial agents, mostly anaerobic [7], triggers the process when a genetic susceptibility exists [10].

b) An inappropriate, intense and prolonged inflammatory response of the bowel ensues. This inflammatory process involves an initial leukocyte activation and intravascular accumulation, adhesion, transendothelial migration and release of various inflammatory mediators as well. as toxic molecules (cytokines, -cell-adhesion molecules, nitric oxide, reactive oxygen species),

resulting in tissue injury [6, 7,9, 10].

Inflammatory cell recruitment in CD involves enhanced binding of leucocytes to mucosal microvascular endothelial cells [11].

The adhesion process begins with the interaction between $b_2$ integrins and selectins present on

neutrophils and endothelial cells respectively [12]. Bonding between selectins and their ligands, occurs simultaneously with bonding between integrins on neutrophils and intercellular and vascular adhesion molecules (ICAM - VCAM), members of the immunoglobulin (Ig) super family, present on the endothelial cells [12,13,14]. Proinflammatory cytokines (TNF-a, IL-1, IL-6), nitric oxide synthase (NOS) activity, leucotrienes, prostaglandins and other metabolites also modify the tissular lesion directly [15].

**Microvascular Dysfunction.**

Recent studies provide evidence that vascular occlusion may be important in the pathogenesis of CD Impairment of capillary blood flow in the colonic mucosa due to arteriolar microthrombosis at the level of the muscularis propria is a fundamental disturbance in CD [7, 8, 9, 10].

The short vessels supplying the mesenteric margin are end-arteries, consequently any pathological occlusion leads to regional ischemia [16].

Patients with active CD also show a significant higher fibrinogen fractional concentration than controls or patients with inactive CD [7].

*CD therapy*

The therapy of CD depends on the disease stage and the severity index (Crohn's Disease

Activity Index -CDAI) of the disease according to appropriate scales [17, 18].

General measures include improvement of overall nutrition, intestinal disease treatment

and local interventions.

Therapeutic modalities used in CD management can be divided into several main categories:

corticosteroids - a main stay for many years, aminosalicylates [sulfalazine, 5-aminosalicylic acid (5-ASA)], immunomodulatory agents [ azathioprine, 6-mecaptopurine (6-MP) ,methotrexate and others], antibiotics [quinolones, metronidazole] [17, 18].

Perineal and fistulizing CD often require surgical treatment. Surgical interventions may temporarily alleviate the present fistulae and abscesses but may not influence or improve the underlying disease [9].

Novel investigational agents as heparin, IL-10 but mainly an anti-tumor necrosis factor monoclonal antibody (anti-TNF alpha) are considered the new promising therapeutic strategies against CD [9, 17, 18]. HBOT is described as an adjunctive therapy for healing of perianal manifestations of CD [18].

**Rationale for HBO use in Crohn’s disease**

The rationale for using HBOT in patients with CD is related to the clinical and experimental observations regarding the pathogenesis of this Inflammatory Bowel Disease (IBD).

It is now believed, that HBO besides it's known pathophysiological tissular interferences, such as the enhancement of phagocytic killing through the oxygen burst or the promotion in wound healing by fibroblast proliferation [19], affects also the immunological and rheological disorders of the CD. In view of the above effects the following main therapeutic goals are targeted:

a. Microbial agents

HBO is known to establish bacteriostatic or even bactericidal effect producing reactive oxygen species (ROS) when used versus anaerobic bacteria [20]. Inhibition of amino acids and protein biosynthesis in aerobic bacteria by HBO has also been demonstrated [21].

Tissue $P0_2$ restoration through HBO acts as a stimulus to enhance intraphagocytic synergism in PMN leucocytes. Beyond the "oxidative burst" improvement in itself, ROS and intracellular present antibiotics - typically quinolones - are acting synergistically.

If superoxide anion production is diminished, quinolones, an important therapeutic agent in CD, exhibits a significantly reduced antibacterial action [21].

Furthermore HBO may act synergistically with other antibiotics used in CD, e.g. metronidazole, playing the role of a bactericidal agent, able to improve wound margin and thus permitting surgical closure [5].

b. Inflammatory process

The blocking of enhanced binding of leucocytes to mucosal capillary microvascular endothelial cells in CD is an important therapeutic goal for hyperbaric medicine [12]. Studies, aimed at characterizing the molecular determinants of leucocyte recruitment in mucosal biopsy specimens from patients with CD, have shown an increased expression of $b_2$ integrins on neutrophils and ICAM-1 on endothelial cells [12, 13].

It is now established, both by experimental and clinical studies, that HBO inhibits the function of $b_2$ integrins [22]. This process is linked to impaired synthesis of cGMP by HBO [23]. Furthermore HBO has been recently found (February 2000) to down regulate ICAM expression induced by hypoxia in an endothelial cell model [24].

Additionally, in CD, leucocytes are stimulated by ligands as FMLP (N4ormyl-methionyl-leucine phenylaline), a peptide produced by intestinal bacteria and present in the colonic lumen. It has been shown that in patients with active CD the circulating neutrophils exhibit an increased number of FMLP-receptors [25]. HBO inhibits the neutrophil response to FMLP [23].

Proinflammatory cytokines as TNF-a, IL-1 and IL-6, when measured in patients with CD, are elevated in the active stage of the disease, and can upregulate expression of selectins [15]. During the HBO therapy the levels of those cytokines decreased and remained low, compared to pretreatment values [23, 24, 26, 27, 28].

VEGF a potent angiogenic vascular permeability enhancing cytokine, - originated from intestinal mucosa, is increased in active CD [29]. It is also known that neutrophils infiltrating inflammed tissues contain VEGF. Experimental studies provide evidence that hyperoxia may downregulate VEGF [30].

Inducible NOS (iNOS) activity, which is raised in patients with inflammatory bowel disease (IBD), is another possible therapeutic target of HBO in CD [31].

Rachmilevitz's experimental study, showed a significant decrease in NO production and prostaglandins levels in IBD post HBO therapy [32].

c. Vascular microthrombosis

Leukocyte adherence to mucosal capillaries, impairs microcirculation. Moreover, NADPH oxidase of leucocytes enhances the overaction of Bowel's mucosa NADPH by synergism, promoting endothelial lesion [33]. HBO prevents microvascular injury, by inhibiting the adhesion of leucocytes to endothelial cells of the capillaries, as mentioned above [22, 23].

The impaired oxygen extraction due to multifocal infarctions in addition to the particular nature of the bowel vascular structure is possibly over ridden by the substantial increased diffusion gradient during HBOT [34].

HBO improves also intracapillary thrombolysis by raising tissue $P0_2$ much over 30 mmHg [35, 36].

**Reported results of HBO therapy (HBOT) for CD**

The use of HBOT in patients with CD was first reported by Brady et al in 1989 (1). The case concerned a patient with progressively worsening perineal CD, who had been refractory to surgery and drug therapy (antibiotics, immunomodulators, 5-ASA agents ) and who responded in HBOT completely.

Since that report 21 other patients with CD have been treated with HBO, for severe or refractory perineal lesions (Table 1).

Of the 22 patients, described in the bibliography, 16 (73%) had a complete response to HBOT, 2 (9%) responded partially and 4 patients (18%) had no response at all (including two drop-outs). All the above patients presented with untreated or retractable and complicated CD cases. A recently published case report [6/1999], confirms the efficacy of HBOT in intractable CD ulcers, without accompanying complications. The patient was a 16 years old girl with enteric ulcers involving the ileocolic region, unresponsive to medical and nutritional treatment. Seven months after successful response to HBOT, the patient continued to be in clinical and endoscopic remission [37].

It's of major interest also, that six patients with CD unresponsive to medical treatment, who have been hospitalized at the Dead Sea level, where an increased barometric pressure exists (increased inspiratory $PO_2$) showed a significant improvement in the perineal and ileocolic lesions of the disease [38].

The side effects of HBOT, in the treated patients, were of minor importance so far. One patient suffered ear barotrauma, two patients were not able to tolerate treatments for psychological reasons, and one suffered temporary blurred vision [5].

The accompanying surgical interventions of all the above patients, took place mainly before HBOT.

## Discussion

The multifactorial pathogenesis of CD remains obscure and it's not surprising that it has been difficult to optimize therapy [9, 17,181.

Up dated gastroenterological articles for CD therapy, declare, that even if a therapy proves effective "do clinicians truly know how it works?" [18].

Challenges in developing new therapeutic strategies include not only identifying novel agents but also improving the definitions of clinical endpoints and determining efficacy at the biological level. HBO is now considered as a therapeutic agent for CD [18], based on the beneficial effects, which have been described in patients with severe or refractory perianal lesions. The reported dramatic response of the majority of severe perianal lesions to HBOT and the updated pathogenetic theories of CD, where HBO may interfere as potential regulator, provide encouraging evidence to enhance the research in this area.

Nevertheless, HBOT might play an equivalently important role in the treatment of CD patients without severe complications, who do not respond to standard therapy, accelerating the effects of steroids, azathioprine or 6-MP [37, 38].

In addition, the enhancement of the healing process might constrain the know side effects from the long-term use of steroids and other immunomodulating agents. However, the number of the involved studies and the varying protocols can’t validate definitely the therapeutic efficacy of HBO in the treatment of this IBD.

There is limited experience as far as prevention of long-term recurrence is concerned, after the original treatment or the repetition of sessions.

Lack of multicenter studies of HBOT for CD also impairs the consensus of the minimum number of sessions, necessary to establish an improvement, in order to show the effectiveness of therapy. Less frequent treatments would be more easily accepted by the chronically stressed patients, being usually in bad psychologic endurance, and would also improve the cost effectiveness of HBOT [38].

## Conclusion

The elucidation of pathogenesis, as well as the existing experience from the use of HBO in CD therapy so far, suggests an acceptable beneficial effect in this IBD. Further clinical trials will be necessary to conclusively validate the basis for HBOT involvement as an adjunctive therapeutic method in CD patients.

According to the above considerations, it can be presumed that HBO could be an accepted part in the CD therapeutic armamentarium, regarding the existing clinical data and the on going research.

**Table 1**

**List of studies including CD patients treated with HBO (summary)**

| Study | Year | P | Lesions | Time | Medication | Surgery | HBOT | Result |
|---|---|---|---|---|---|---|---|---|
| Brady | 1989 | 1 | abscess stricture | 8 yrs | ASA, metronidazole, steroids, ABX, 6- | Proctosigmoidectomy, diversion | 2.4ATA, 2hrs, 67 sessions | CR |
| Nelson | 1990 | 1 | abscess fistula | ? | ASA, metronidazole, steroids azathioprine | colostomy, proctocolostomy | 2ATA, 2hrs, 64 sessions | CR |
| Lavy | 1994 | 1 | abscess fistula | ? | azulfidine | ? | 2.5ATA, 1.5hrs, 20 sessions | CR |
| | | 2 | fistula infiltration | ? | 5-ASA | ? | 2.5ATA, 1.5hrs, 20 sessions | CR |
| | | 3 | fistulae strictures | ? | Azulfidine | ? | 2.5ATA, 1.5hrs, 60 sessions | CR |
| | | 4 | fistula | ? | 5-ASA | ? | 2.5ATA, 1.5hrs, 40 sessions | CR |
| | | 5 | fistula | ? | azulfidine | ? | 2.5ATA, 1.5hrs, 40 sessions | CR |
| | | 6 | fistula | ? | 5-ASA | ? | 2.5ATA, 1.5hrs, 40 sessions | PR |
| | | 7 | fistula | ? | azulfidine | ? | 2.5ATA, 1.5hrs, 20 sessions | CR |
| | | 8 | fistulae | ? | azulfidine | ? | 2.5ATA, 1.5hrs, 60 sessions | CR |
| | | 9 | fistulae | ? | 5-ASA | ? | 2.5ATA, 1.5hrs, 60 sessions | PR |
| | | 10 | fistulae | ? | none | ? | 2.5ATA, 1.5hrs, 60 sessions | CR |
| Colom-bel | 1995 | 1 | fissure, fistula | 2 yrs | azathioprine, 5-ASA, zinc | Local treatment | 2.5ATA, 2hrs, 36 sessions | PR NR |
| | | 2 | fissure fistula | 6 mo | azathioprine, 5-ASA, zinc | ileocolectomy, local treatment, | 2.5ATA, 2hrs, 30 sessions | NR |
| | | 3 | fistula | 4 yrs | metronidazole TPN | Colectomy, proctocolectomy | 2.5ATA, 2hrs, 30 sessions | NR |

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|---|---|---|---|---|---|---|---|---|
| | | 4 | wound | 6 yrs | metronidazole, azathioprine | proctocolectomy | 2.5ATA, 2hrs, 40 sessions | PR-55s CR |
| | | 5 | ulcer, fistula | 27 mo | metronidazole | local treatment | 2.5ATA, 2hrs, 36 sessions | CR |
| | | 6 | ulcer, fistula | 4 yrs | metronidazole, azathioprine | ileal section | 2.5ATA, 2hrs, 40 sessions | CR |
| | | 7 | fissure, fistula | 3 mo | 5-ASA | colectomy, colostomy | 2.5ATA, 2hrs, 33 sessions | CR |
| | | 8 | fissure, fistula | 2 mo | 5-ASA | local treatment | 2.5ATA, 2hrs, 31 sessions | CR |
| | | 9 | ulcer stricture | 10 yr | metronidazole, azathioprine | hemicolectomy, colostomy | not complete | NR |
| | | 10 | fissure fistula | 2 yrs | metronidazole ASA | local | not complete | NR |
| Total | | 22 | CR = 16 | | NR = 4 | PR = 2 | | |

CR = complete response, NR = no response, PR = partial response

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